National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Nivolumab for treating metastatic or unresectable urothelial cancer [ID995]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment: the draft remit

Section	Consultee/ Commentator	Comments	Action
Wording	BMS	The draft remit is appropriate.	Comment noted.
	NCRI-ACP-RCP-RCR-BUG	Yes no additional comments	Comment noted.
	Urology foundation	Yes	Comment noted.
Timing Issues	BMS	Patients with metastatic or unresectable urothelial cancer who have failed platinum-based therapy have a very poor prognosis, with no approved treatment options in the UK. It is important for NICE to provide a recommendation for the use of nivolumab within the NHS as close to marketing authorisation as possible, given the limited effective treatment options currently available to patients.	Comment noted. The topic will be scheduled to align as closely as possible with the expected marketing authorisation dates.
	NCRI-ACP-RCP-RCR-BUG	FDA approval granted in this setting Feb 2017.	Comment noted.

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	Urology foundation	Bladder cancer patients need access to new & more effective treatments now	Comment noted.

Comment: the draft scope

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Background information	BMS	Over all the summary is well written. However, in the introductory paragraph it may be helpful to state clearly that TCC is the same as urothelial cancer to avoid potential confusion. Similarly, the reference to the incidence of TCC as a form of kidney could be worded better to maintain the focus on urothelial cancer.	Comment noted. The background section of the scope is only intended to briefly describe the disease, prognosis associated with the condition, epidemiology and alternative treatments currently used in the NHS.
	NCRI-ACP-RCP-RCR-BUG	We would add more detail to this section regarding prognosis. Approximately 25% of patients with muscle-invasive bladder cancer present with or later develop metastases. Although initial response rates are high median survival with multiagent chemotherapy is approximately 15 months with a 5 year	Comment noted. The background section of the scope is only intended to briefly describe the disease,

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		survival rate of 5%. Second line chemotherapy has only a limited role.	prognosis associated with the condition, epidemiology and alternative treatments currently used in the NHS.
The technology/ intervention	BMS	The technology could be more comprehensively described as follows: "Nivolumab is a fully humanised monoclonal immunoglobulin (IgG4) antibody that specifically binds to PD-1 receptor on the surface of immune cells and restores T-cell activity by blocking the inhibitory pathway with PD-L1".	Comment noted. The scope has been amended where appropriate to reflect this description of the technology.
	NCRI-ACP-RCP-RCR-BUG	Nivolumab is an IgG4 PD-1 immune checkpoint inhibitor antibody. 2 trials have published preliminary results, FDA approval has been granted on response rates alone.	Comment noted.
Population	BMS	Yes, the population is appropriately defined.	Comment noted.
	NCRI-ACP-RCP-RCR-BUG	Yes. At present PDL1 expression has not been associated with response rates.	Comment noted.
Comparators	BMS	As highlighted in the background section, current (2015) NICE guidelines for the diagnosis and management of bladder cancer [NG2] provide an overview of the treatment recommendations for patients in the second-line setting. These include re-challenge with first-line cisplatin-based treatment for certain patients. Given, however, the scope of this appraisal is focused on patients whose disease has progressed after prior platinum-containing chemotherapy,	Comment noted. At a scoping workshop for ID939 (Atezolizumab for treating locally advanced or metastatic

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		it is unlikely that re-treatment with first line platinum-based therapies are an appropriate comparator set. Scoping consultation comments as part of ID1019 from professional associations indicated that there is no best alternative care and that either paclitaxel or docetaxel are used as the standard in patient population who have progressed on/after platinum-containing chemotherapy.	urothelial carcinoma) it was noted that there is a proportion of people who would be retreated following progression if they previously had a good response to platinum-based chemotherapy, or who receive best supportive care but would wish to receive an active treatment if they could tolerate it. No change made to the scope.
	NCRI-ACP-RCP-RCR-BUG	Comparators listed are current standard although all with a limited role. Consider including the other immunotherapy drugs currently being investigated Atezolizumab and Pembrolizumab.	Comment noted. It has been indicated that other immunotherapy drugs are not currently standard of care in England, and are therefore not included as comparators.
	Roche	Atezolizumab is currently under appraisal by NICE for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior	Comment noted. Comparators must be

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		chemotherapy or who are considered cisplatin ineligible. Atezolizumab should be included within the appraisal scope as it has the potential to become standard of care in the UK, replacing the comparators as listed within this scope	treatments which are the current standard of care in England, and therefore other immunotherapy drugs are not included as comparators.
Outcomes	BMS	Yes.	Comment noted.
	NCRI-ACP-RCP-RCR-BUG	Yes	Comment noted.
	Urology foundation	Yes	Comment noted.
Economic analysis	BMS	A lifetime horizon will be adopted to ensure all associated costs and benefits are accurately captured.	Comment noted.
Equality and Diversity	BMS	No equality issues have been identified.	Comment noted.
	NCRI-ACP-RCP-RCR-BUG	No	Comment noted.
Innovation	BMS	Nivolumab is a fully humanised monoclonal immunoglobulin (IgG4) antibody that specifically binds to PD-1 receptor on the surface of immune cells and restores T-cell activity by blocking the binding of the PD-L1 and PD-L2 ligands found at the tumour site to PD-1 receptors on immune cells. This	Comment noted. The company have the opportunity to make the case for innovation in its

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		approach, enabling the body's own immune system to target cancer, is a novel approach in treating urothelial cancer and has the potential to offer significant survival and safety benefits to patients compared to chemotherapy.	submission. No changes to the scope required.
	NCRI-ACP-RCP-RCR-BUG	Nivolumab was approved by the FDA in February 2017. Two trials should be included in appraisal CheckMate 032 Sharma t al Lancet Oncol. 2016 Nov;17(11):1590-1598. CheckMate 275 Sharma et al Lancet Oncol 2017 This trial reports varying RR dependent on PDL1 expression between 16.1%-28.4%. An acceptable safety profile was noted, but follow up is on going with no other endpoints reported as yet.	Comment noted.
	Urology foundation	Anything that might lead to greater chance of recovery or longer survival rates will be welcomed by bladder cancer patients. There have been few new treatments for this disease.	Comment noted.
Other considerations	-	-	-
Questions for consultation	BMS	1) Should atezolizumab and pembrolizumab be considered as comparators? No. As these drugs are neither licenced nor reimbursed in the UK, they cannot be considered UK standard of care. 2) Are people with PD-L1 positive tumours more likely to benefit from this	Comments noted. 1. Other immunotherapy drugs will not be considered as comparators.

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		treatment? As noted in the 'Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)' for ID939, PDL-1 positive and PDL-1 negative subgroups were removed from the scope – due to a lack of mature and consistent data. 3) Where do you consider nivolumab will fit into the existing NICE pathway Bladder cancer? It is expected that nivolumab would be a treatment option for patients with metastatic or unresectable urothelial cancer whose disease has progressed after platinum-based chemotherapy, in line with the proposed remit of this appraisal.	2. PD-L1 positive subgroups will not be included as a subgroup in the final scope. If the committee consider this subgroup to be relevant for its decision-making it may request additional evidence during the appraisal process. 3. No change required to the scope.
	NCRI-ACP-RCP-RCR-BUG	Consider widening appraisal to combination of immunotherapy and chemotherapy in newly diagnosed patients.	Comment noted. NICE considers that the combination of the technology with chemotherapy is outside of the remit of this appraisal.
	Roche	1. Atezolizumab and pembrolizumab should be included within the appraisal scope, as these products are currently under appraisal and have the potential to become UK standard of care, replacing the comparators as listed within this scope. 2. Best supportive care can be defined as the basket of symptomatic and supportive treatments designed to enhance comfort and quality of life but	Comments noted. 1. Comparators must be treatments which are the current standard of

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		not delivered with the primary intention or expectation of prolonging life, for example pain relief. Active anti-tumour treatments are excluded by this definition. 3. Appropriate 4. Subgroup analyses are challenging without phase III, randomised, controlled, clinical trial evidence 5. Assessing the impact of response in PDL1 positive patients is challenging without phase III, randomised, controlled, clinical trial evidence. 6. No comment 7. No comment 8. Atezolizumab, a PDL1 inhibitor, is anticipated to receive marketing authorisation in 2017 for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy or who are considered cisplatin ineligible. Atezolizumab as the first PDL1 inhibitor was granted break through designation by the FDA and a promising innovative medicines (PIM) status by the MHRA, as well as approved under the Early Access to Medicines (EAMS) scheme. As such, nivolumab is not anticipated to offer a step change in the treatment of mUC. 9. No comment 10. No comment 11. Appropriate to appraise via the STA process	care in England, and therefore other immunotherapy drugs are not included as comparators. 2. Comment noted. 4, 5. PD-L1 positive subgroups will not be included as a subgroup in the final scope. If the committee consider this subgroup to be relevant for its decision-making it may request additional evidence during the appraisal process. 8. Comment noted. 11. Comment noted.
Additional comments on the draft scope	-	-	-

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
NHS England